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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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LAW OFFICES OF [illegible]
P O BOX 450
ALAMEDA CA 94501

EXAMINER	
[illegible]	
ART UNIT	**PAPER NUMBER**
1745	7

DATE MAILED: 09/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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PTO-90C (Rev. 2/95)
*U S GPO 2000-473-000/44602

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/412,297	TING, KANG	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 1999*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8-12* is/are pending in the application.

4a) Of the above claim(s) *3-7 and 13-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
18)☐ Interview Summary (PTO-413) Paper No(s). _____.
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the reasons set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

APPLICANT MUST RESPOND IN THE SAME TIME PERIOD SET FOR RESPONSE TO THIS OFFICE ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

2. Applicant's election with traverse of Group I, claims 1-2 and 8-12 in Paper No. 7 filed on June 11, 2001 is acknowledged. Groups II-XI are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being to a non-elected invention.

The traversal is on the grounds that Groups I-XI are not independent and distinct, therefore the examination of the entire application does not constitute a serious

burden. These arguments have been fully considered but are not found to be persuasive for the reasons below:

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct patented inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each (see MPEP 802.01). In the instant situation, the inventions of Groups I-XI are drawn to distinct inventions which are separate products and methods capable of separate manufacture, use or sale as described in the previous Office Action.

Classification of the subject matter is merely one indication of the burdensome nature of the search. The literature search, particularly relevant in this art, is not co-extensive, because for example, Groups I-XI are drawn to different methods which require different method steps, parameters and endpoints. Groups XI is drawn to a product. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification Objections

3. The specification is objected because of the following informalities:

Page 11, line 20, "in by changes" should be deleted.

Drawings

4. The drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 948.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "change." It is unclear as to what the applicant is referring? Clarification is required.

6. Claims 1-2 and 11-12 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-2

and 11-12 recites "test agent". It is unclear as to what the applicant is referring? Clarification is required.

7. Claim 1 and 2 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 2 recites "alter or alters". It is unclear as to what the applicant is referring? Clarification is required.

8. Claim 2 is vague and confusing because it recites both "recording test agents that alter the expression of the Nell-1 nucleic acid or the Nell-1 protein"; however, these appear to be the same thing. Altering the expression of the gene would inherently alter the expression of the protein. Accordingly, this language appears to be redundant. For purposes of this Office Action, the claim language has been interpreted as altering the expression of gene. If this assumption is correct, then the phrase "or the Nell-1 protein" should be deleted from the claim. Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1 and 8-12 are rejected under 35 U.S.C. 35 U.S.C. 103(a) as being unpatentable over Kuberasampath et al *(U. S. Patent No. 5,674,844, published October 7, 1997)* further in view of Ting et al *(The Journal of Bone and Mineral Research, Volume 14, Number 1, January, 1999).*

Claims 1 and 8-12 are drawn to a method of screening for an agent that alters bone mineralization comprising contacting a Nell-1 gene with a test agent and detecting a change in the expression level of Nell-1 gene in a cell that is not contacted with said test agent where a diference of the Nell-1 gene in the cell that is not contacted with said test agent where a difference in the expression level of Nell-1 in the contacted cell and the cell that is not contacted indicates that is not contacted indicates that said agent modulates bone mineralization.

Kuberasampath et al teach a method of screening for candidate compounds with alter bone mass or preventing bone loss (i.e. bone mineralization). Kuberasampath et al teach candidate compounds that may alter the expression of morphogens by incubating the cell in culture with the compound in order to assess the effects of the compound on the cell. Kuberasampath et al that this can be accomplished by detection of the morphogen either at the protein or RNA level (columns 36-38).

Kuberasampath et al do not specifically teach assay methods for testing compounds which effect the expression of the Nell-1 gene.

Ting et al teach human Nell-1 expressed in Unliteral Coronal Synostosis (UCS) Ting et al teach a method of screening by demonstrating that DD-PCR can be applied to identify genes up or down-regulated in Unliteral Coronal Synostosis. The DD-PCR screening process was used to detect the Nell-1 PCR product in a normal cranial suture and an abnormal cranial suture on four UCS patients. Ting et al teach that the PCR products were analyzed on a 1% agarose gel and confirmed by Southern blotting using the labeled cDNA clone as a probe (page 82). Ting et al teach the identification of cells expressing Nell-1 within the suture site using *in situ* hybridization. Ting et al teach that human multi-organ tissue mRNA blot showed that the Nell-1 was expressed in rat calvarial osteoprogenitor cells and was largely absent in rat tibiae and fibroblast cell cultures. Ting et al teach that Nell-1 and it related molecules may represent a new class of proteins involved in growth and development. Ting et al demonstrated the increased expressions of Nell-1 in intramembranous bone formation and in the pathological entity of premature UCS (page 88).

It would be *prima facie* obvious to one skilled in the art at the time the invention was made to test for compounds that effect the expression of the Nell-1 gene by contacting a cell containing the Nell-1 gene with a test agent because Kuberasampath et al teaches screening assays for candidate compounds which alter a gene which produces a protein that stimulates bone formation, i.e., bone mineralization. Since the Nell-1 gene, as taught by Ting et al, is also known to produce a protein that enhances bone mineralization it would have been obvious to one of ordinary skill in the art to

screen for compounds which may positively effect expression of the gene and thereby increase bone mass and/or prevent bone loss.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath et al in view of Ting et al as applied to claims above and further in view of Siris et al (Osteoporos Int., 1998).

Claim 2 is drawn to method of claim 1, further comprising recording test agents that alter expression of the Nell-1 nucleic acid or Nell-1 protein in a database of modulators of Nell-1 activity or in a database of modulators of bone mineralization.

Siris et al teach a database the that contains information on several hundred thousand subjects. Siris et al further teach that this database will contain peripheral and central measurements of bone density and relate these factors, treatment patterns and the natural history of osteoporosis.

It would be *prima facie* obvious to one skilled in the art at the time the invention was made to add the modulators of bone mineralization as taught by Kuberasampath et al in combination with Ting et al to the database of Siris et al because Siris et al teach

that the database will provide a resource that is unmatched in size and scope in the medical field and will allow for future research in a number of areas including patient outcomes, types of follow-up employed in clinical practice, diagnostic cost modeling and osteoporosis therapy use (see Abstract).

Pertinent Prior Art

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *Liu et al, Developmental Biology, Volume 166, 1994, 220-234 and Gelbart et al, Science, Volume 282, October 23, 1998).*

Status of Claims

12. No claims are allowed.

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner

JENNIFER E. [illegible]
PRIMARY EXAMINER

Application No. 09/412297

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CAR §1.821 - §1.825 for the following reasons(s):

[X] 1. This application clearly fails to comply with the requirements of 37 CAR §1.821 - §1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990, and at 55 FR 18230, May 1, 1990.

[ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CAR §1.821(c).

[ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CAR §1.821(e).

[ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CAR §1.822 and/or §1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing".

[ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CAR §1.825(d).

[ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CAR §1.821(e).

[ ] 7. Other: _____

APPLICANT MUST PROVIDE:

[X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

[X] An initial or substitute paper copy of the "Sequence Listing", as were as an amendment directing its entry into the specification.

[X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CAR §1.821(e) or §1.821(f) or §1.821(g) or §1.825(b) or §1.825(d).

FOR QUESTIONS REGARDING COMPLIANCE WITH THESE REQUIREMENTS, PLEASE CONTACT:

For Rules Interpretation, call (703) 308-1123
For CRF Submission help, call (703)308-4212
For Patentin Software help, call (703) 557-0400

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE.